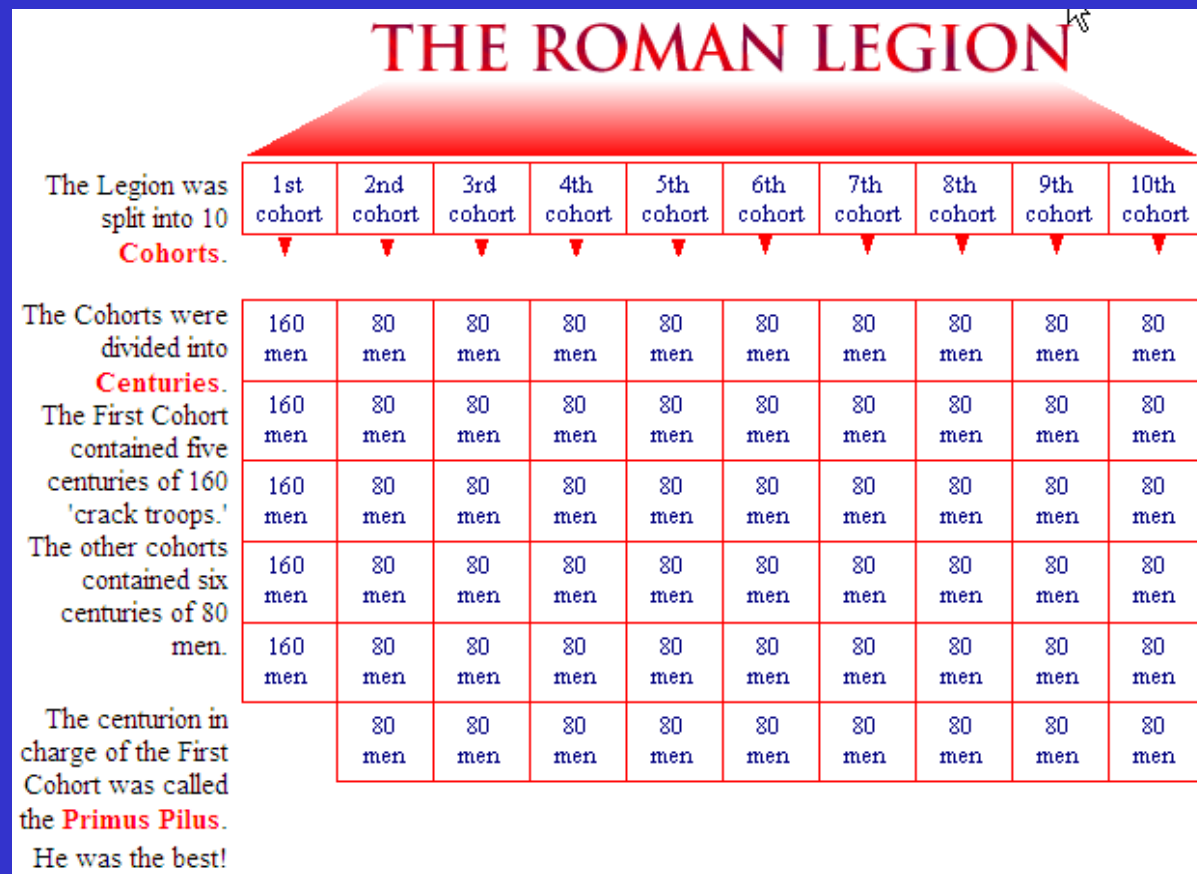# Cohort Studies

Figure 1: **An early cohort in search of favourable outcomes**

Madhukar Pai, MD, PhD
McGill University

Montreal

Cohort: origins of the word

THE ROMAN LEGION

	1st cohort	2nd cohort	3rd cohort	4th cohort	5th cohort	6th cohort	7th cohort	8th cohort	9th cohort	10th cohort
The Legion was split into 10 **Cohorts**.	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼
The Cohorts were divided into **Centuries**.	160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
The First Cohort contained five centuries of 160 'crack troops.'	160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
	160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
The other cohorts contained six centuries of 80	160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
men.	160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
The centurion in charge of the First Cohort was called the **Primus Pilus**. He was the best!		80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men

2

Introduction

- Measurement of the occurrence of events over time is a central goal of epidemiologic research

- Regardless of any particular study design or hypothesis, interest is ultimately in the disease or outcome-causing properties of factors that are <u>antecedent</u> to the disease or outcome.

- All study designs (including case control and cross-sectional studies) are played out in some populations over time (either well defined cohorts or not)

  - They differ in how they acknowledge time and how they sample exposed and non-exposed as these groups develop disease over time

All the action happens within a "sea of person-time" in which events occur
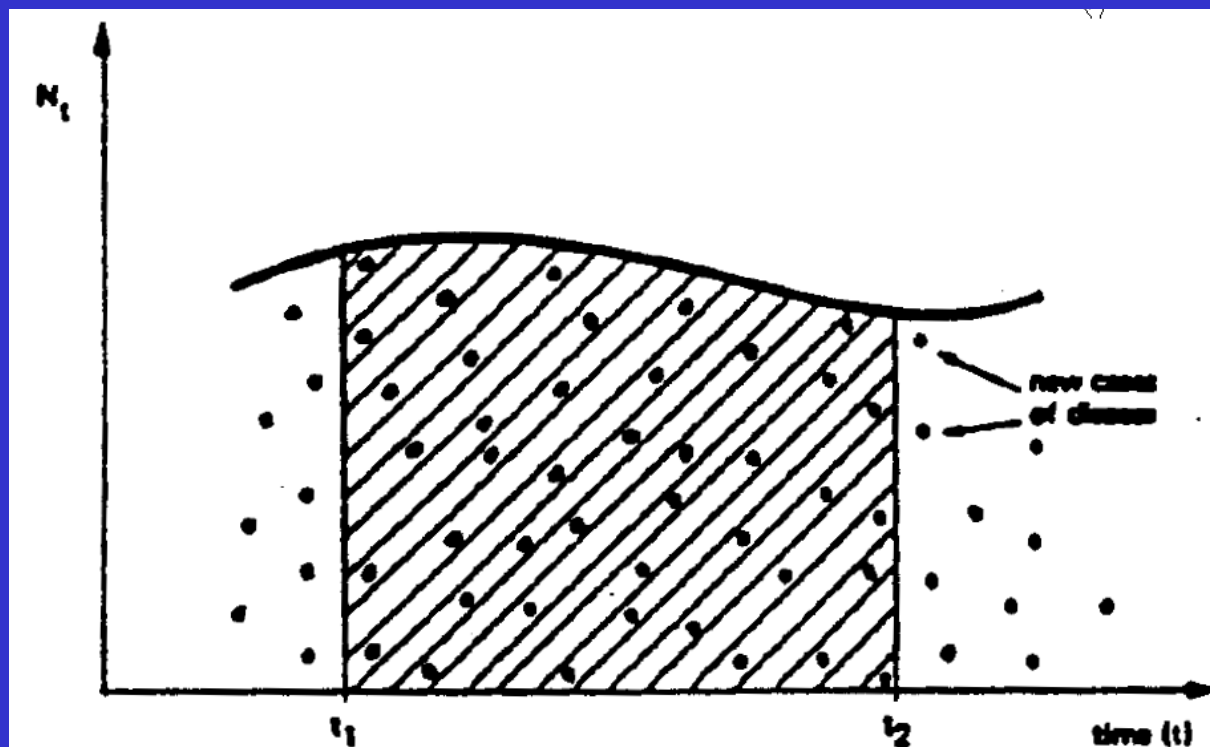
FIGURE 2 Graphical illustration of the occurrence of new (incident) cases over time in a candidate population (of size N_t at time t)

Morgenstern IJE 1980

Cohort studies

Intuitive approach to studying disease incidence and risk factors:

1. Start with a population at risk

2. Measure exposures and covariates at baseline

3. Follow-up the cohort over time with
   a) Surveillance for events or b) re-examination

4. Keep track of attrition, withdrawals, drop-outs and competing risks

5. For covariates that change over time, measure them again during follow up

6. Compare event rates in people with and without exposures of interest
   - Incidence Density Ratio (IDR) is the most natural and appropriate measure of effect
   - Adjust for confounders and compute adjusted IDR
   - Look for effect measure modification, if appropriate

Cohort studies

- Can be large or small
- Can be long or short duration
- Can be simple or elaborate
- Can look at multiple exposures and multiple outcomes
- Can look at changes in exposures over time
- For rare outcomes need many people and/or lengthy follow-up
- Are usually very expensive because of the numbers and follow-up requirements
- But once a cohort is established, can sustain research productivity for a long, long time!
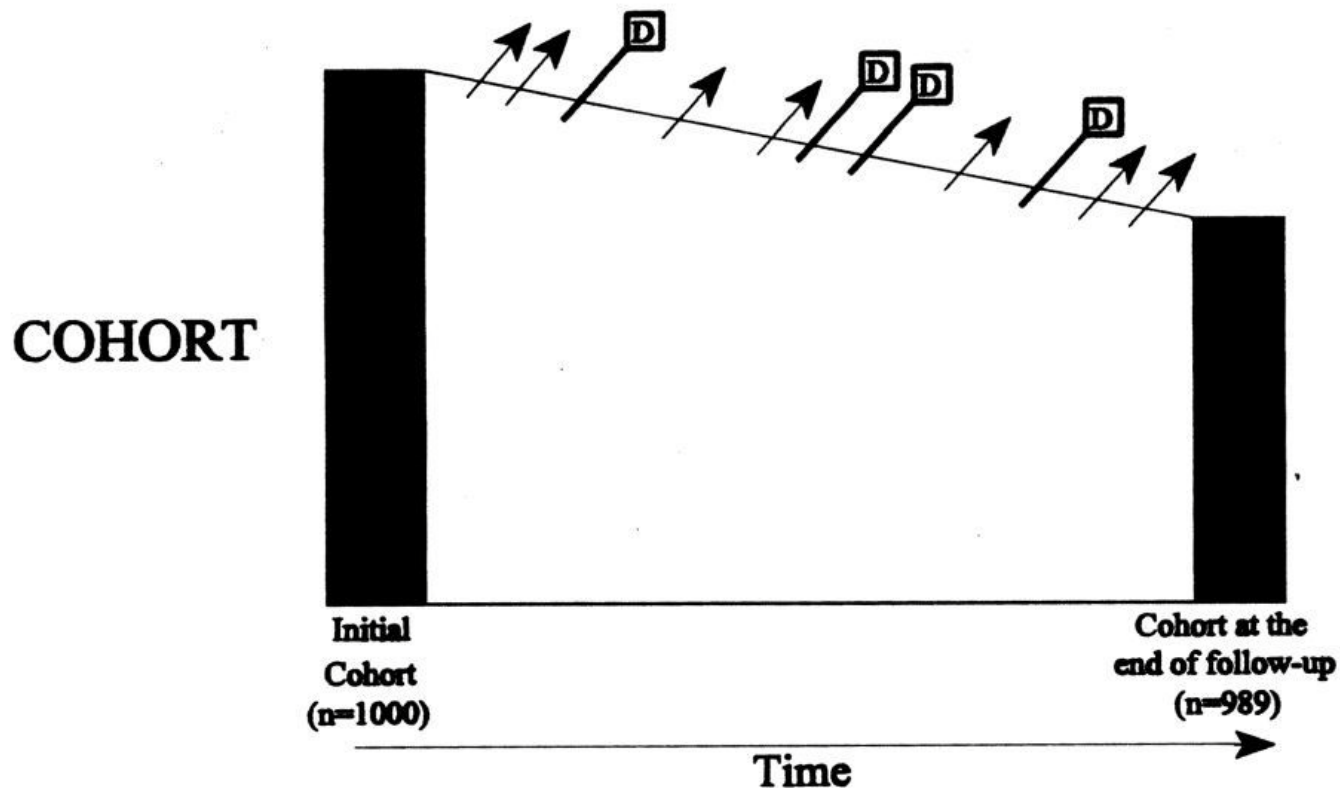
Cohort: keeping track of people

COHORT

Initial
Cohort
(n=1000)

Cohort at the
end of follow-up
(n=989)

Time

Figure 1–13 Diagram of a hypothetical cohort of 1000 subjects. During the follow-up, four disease events (D) and seven losses to follow-up (arrows) occur, so that the number of subjects under observation at the end of the follow-up is 989.

Cohort study
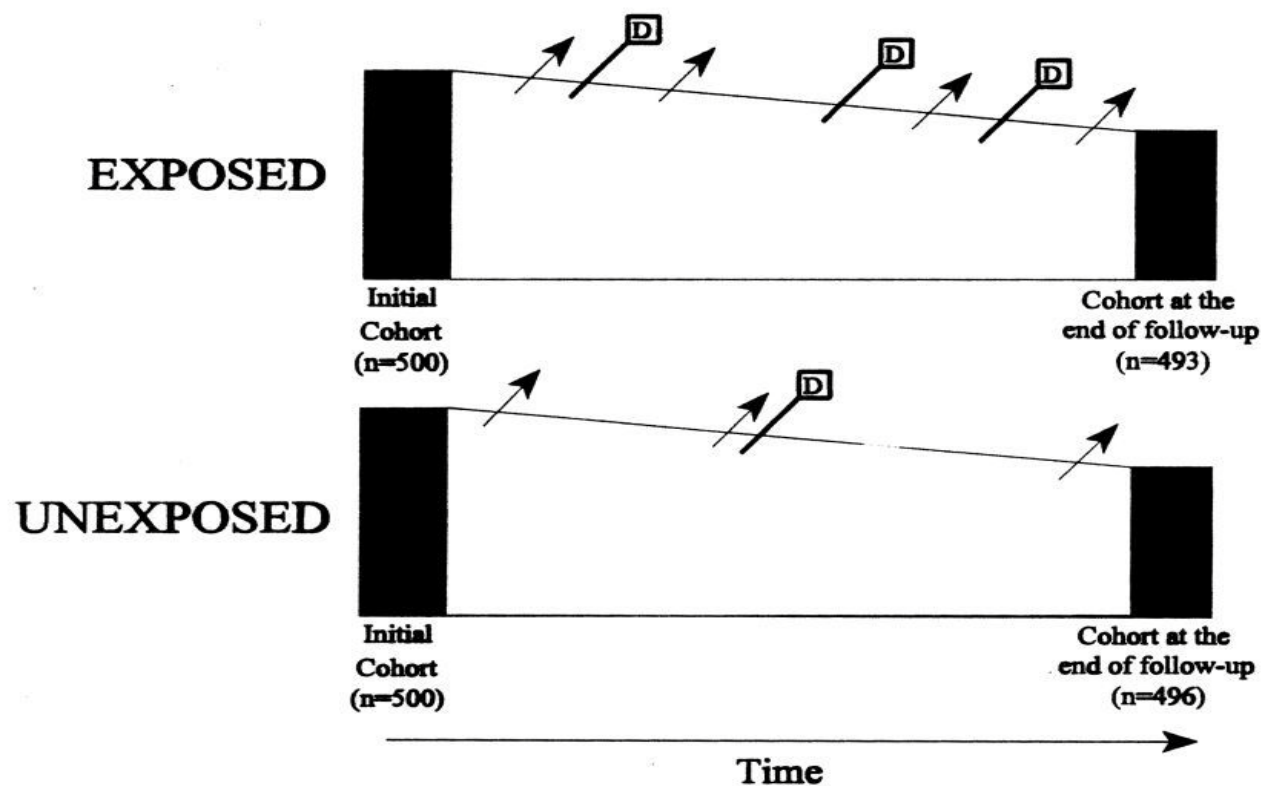
Figure 1–15 Same cohort study as in Figure 1–13, but the ascertainment of events and losses to follow-up is done separately among those exposed and unexposed.

Cohort study: direction of analysis goes from exposure to outcome (even if outcomes have already occurred)
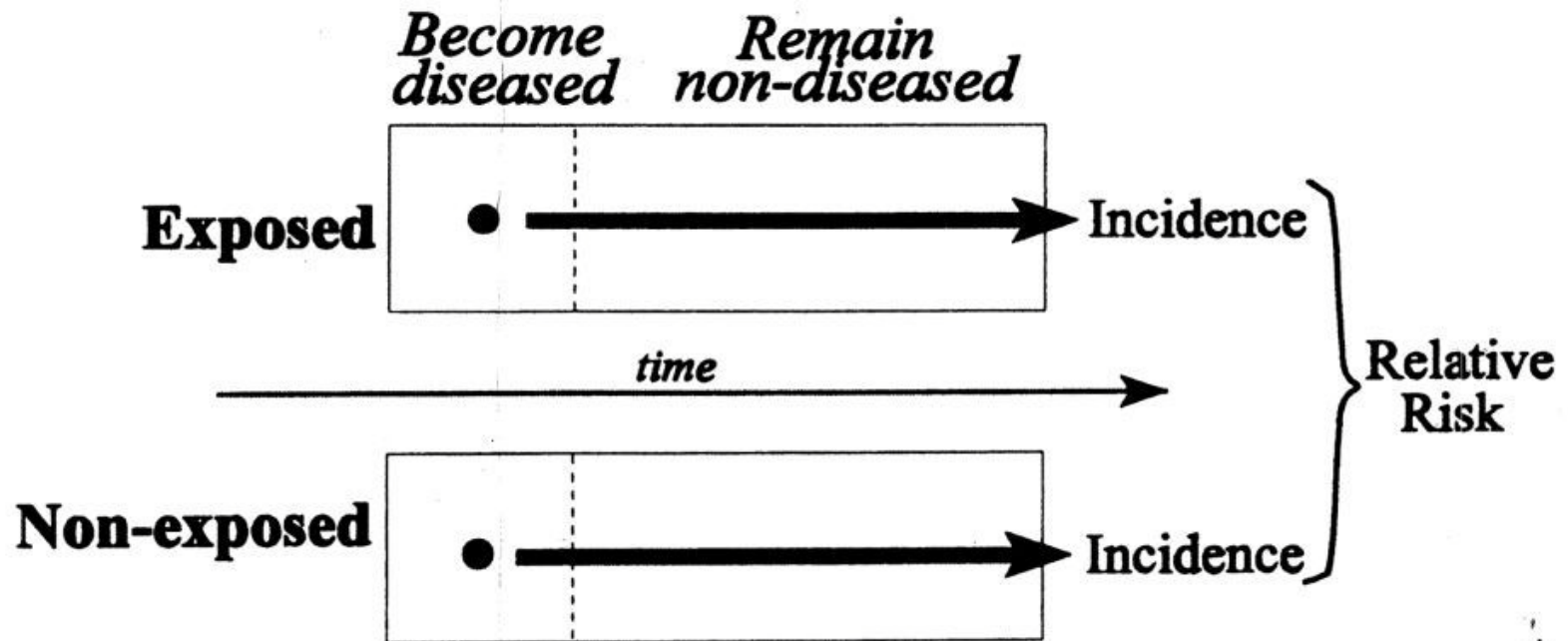
Figure 1-14 Basic analytical approach in a cohort study.

General structure of a cohort study

- The passage of time is explicitly incorporated (difference between beginning and end of the study)
- Observations are made on an outcome of interest (death, incidence of disease, change in a biologic marker, health status)
  - These measures may be made repeatedly throughout the study or only at the beginning and end
- The purpose of the study may be:
  - Focused: to test a specific hypothesis or
  - Descriptive: to gather data with which to generate hypotheses
  - Broad: to test multiple hypotheses
- One strong advantage of a cohort study over other designs is that the dynamic nature of many risk factors and their relationships in time to disease occurrence can only be captured in the cohort design
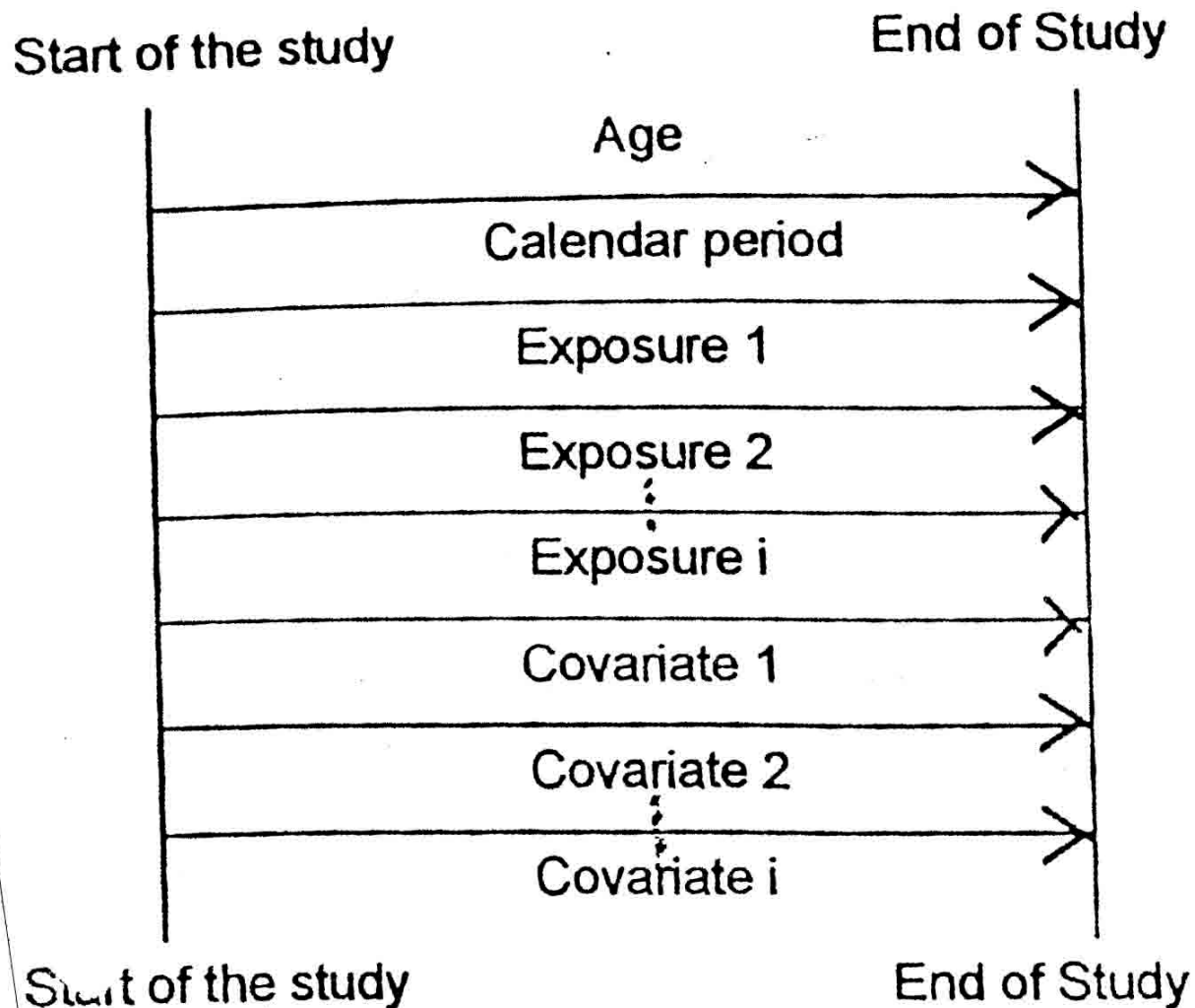
10

FIGURE 1.   The multiple dimensions of time in a cohort study.

Table 1. Types of outcomes for cohort

Discrete events

    Single Events

        Mortality

        First occurrence of a disease or health-related outcome

            Incidence (density)

            Cumulative incidence (risk)

            Ratios (incidence density and cumulative incidence)

    Multiple occurrences:

        Of disease outcome

        Of transitions between states of health/disease

        Of transitions between functional states

Level of a marker for disease or state of health

Change in a functional/physiologic/biochemical/anatomic marker for disease or health

    Rate of Change

        Patterns of growth and/or decline

        "Tracking" of markers of disease/health

    Change in level with time (age)

How are cohorts assembled or identified?

- By geographical region
  - E.g. Framingham heart study
- By occupational group
  - Nurses health study
  - British Doctor's health study
  - Gold miners study on TB in S Africa
- By disease
  - Multi-center AIDS Cohort (MACS)
- By risk groups
  - San Francisco Men's Health Study (gay men)
  - IV Drug Users cohort (ALIVE Study in Baltimore - AIDS Linked to the Intravenous Experience)
- By exposure event
  - Japanese Atomic Bomb Survivors
  - 9/11 FDNY workers cohort

13

How are cohorts assembled or identified?

- Often, researchers begin with a large cross-sectional study (e.g. survey)

- They then go back and re-survey the same population after a time period

- This converts a cross-sectional into a cohort design

Mycobacterium tuberculosis Infection in Health Care Workers in Rural India
Comparison of a Whole-Blood Interferon γ Assay With Tuberculin Skin Testing

Madhukar Pai, MD, PhD
Kaustubh Gokhale, MD
Rajnish Joshi, MD
Sandeep Dogra, MD
Shriprakash Kalantri, MD, MPH
Deepak K. Mendiratta, MD
Pratibha Narang, MD
Charles L. Daley, MD
Reuben M. Granich, MD, MPH
Gerald H. Mazurek, MD
Arthur L. Reingold, MD
Lee W. Riley, MD
John M. Colford, Jr, MD, PhD

AN ESTIMATED ONE THIRD OF the world's population is infected with *Mycobacterium tuberculosis*,[1] presenting a major impediment to tuberculosis control. Despite the importance of latent tuberculosis infection (LTBI), the tubercu-

Context *Mycobacterium tuberculosis* infection in health care workers has not been adequately studied in developing countries using newer diagnostic tests.

Objectives To estimate latent tuberculosis infection prevalence in health care workers using the tuberculin skin test (TST) and a whole-blood interferon γ (IFN-γ) assay; to determine agreement between the tests; and to compare their correlation with risk factors.

Design, Setting, and Participants A cross-sectional comparison study of 726 health care workers aged 18 to 61 years (median age, 22 years) with no history of active tuberculosis conducted from January to May 2004, at a rural medical school in India. A total of 493 (68%) of the health care workers had direct contact with patients with tuberculosis and 514 (71%) had BCG vaccine scars.

Interventions Tuberculin skin testing was performed using 1-TU dose of purified protein derivative RT23, and the IFN-γ assay was performed by measuring IFN-γ response to early secreted antigenic target 6, culture filtrate protein 10, and a portion of tuberculosis antigen TB7.7.

Main Outcome Measures Agreement between TST and the IFN-γ assay, and comparison of the tests with respect to their association with risk factors.

Results A large proportion of the health care workers were latently infected; 360 (50%) were positive by either TST or IFN-γ assay, and 226 (31%) were positive by both tests. The prevalence estimates of TST and IFN-γ assay positivity were comparable (41%; 95% confidence interval [CI], 38%-45% and 40%; 95% CI, 37%-43%, respectively). Agreement between the tests was high (81.4%; κ=0.61; 95% CI, 0.56-0.67). Increasing age and years in the health profession were significant risk factors for both IFN-γ assay and TST positivity. BCG vaccination had little impact on TST and IFN-γ assay results.

JAMA 2005

Serial Testing of Health Care Workers for Tuberculosis Using Interferon-γ Assay

Madhukar Pai, Rajnish Joshi, Sandeep Dogra, Deepak K. Mendiratta, Pratibha Narang, Shriprakash Kalantri, Arthur L. Reingold, John M. Colford, Jr., Lee W. Riley, and Dick Menzies

Divisions of Epidemiology and Infectious Diseases, School of Public Health, University of California, Berkeley; Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco, California; Departments of Medicine and Microbiology, Mahatma Gandhi Institute of Medical Sciences, Sevagram, India; and the Montreal Chest Institute, McGill University, Montreal, Quebec, Canada

AJRCCM 2006

Methods to define exposure and outcome status

- Existing records
  - Occupational (e.g. employee health records)
  - Medical/pharmacy records
  - Vital registration records (births, deaths)
  - Census records
  - Medicare database and the like
- Interviews/questionnaires
- Direct measurements on participants (e.g. periodic health exams and tests)

Asthma Diagnosed after 11 September 2001 among Rescue and Recovery Workers: Findings from the World Trade Center Health Registry

Katherine Wheeler,[1] Wendy McKelvey,[1] Lorna Thorpe,[1] Megan Perrin,[1] James Cone,[1] Daniel Kass,[1] Mark Farfel,[1] Pauline Thomas,[2] and Robert Brackbill[3]

[1]New York City Department of Health and Mental Hygiene, New York, New York, USA; [2]New Jersey Medical School, UMDNJ, Newark, New Jersey, USA; [3]Agency for Toxic Substances and Disease Registry, Atlanta, Georgia, USA

BACKGROUND: Studies have consistently documented declines in respiratory health after 11 September 2001 (9/11) among surviving first responders and other World Trade Center (WTC) rescue, recovery, and clean-up workers.

OBJECTIVES: The goal of this study was to describe the risk of newly diagnosed asthma among WTC site workers and volunteers and to characterize its association with WTC site exposures.

METHODS: We analyzed 2003–2004 interview data from the World Trade Center Health Registry for workers who did not have asthma before 9/11 (n = 25,748), estimating the risk of newly diagnosed asthma and its associations with WTC work history, including mask or respirator use.

RESULTS: Newly diagnosed asthma was reported by 926 workers (3.6%). Earlier arrival and longer duration of work were significant risk factors, with independent dose responses ($p < 0.001$), as were exposure to the dust cloud and pile work. Among workers who arrived on 11 September, longer delays in the initial use of masks or respirators were associated with increased risk of asthma; adjusted odds ratios ranged from 1.63 [95% confidence interval (CI), 1.03–2.56) for 1 day of delay to 3.44 (95% CI, 1.43–8.25) for 16–40 weeks delay.

CONCLUSIONS: The rate of self-reported newly diagnosed asthma was high in the study population and significantly associated with increased exposure to the WTC disaster site. Although we could not distinguish appropriate respiratory protection from inappropriate, we observed a moderate protective effect of mask or respirator use. The findings underscore the need for adequate and timely distribution of appropriate protective equipment and the enforcement of its use when other methods of controlling respiratory exposures are not feasible.

KEY WORDS: asthma, disaster, masks, respirators, World Trade Center, workers. *Environ Health Perspect* 115:1584–1590 (2007). doi:10.1289/ehp.10248 available via *http://dx.doi.org/* [Online 27 August 2007]

as a secondary means of controlling workers' exposure to airborne contaminants, knowing that that no device is fully protective, and that the margin of safety afforded by their use is strongly dependent on selection, fit, and appropriate use (Martyny et al. 2002).

In the aftermath of the WTC disaster, engineering controls clearly were not feasible. Although steps were taken by a number of entities to provide respiratory protection to workers, adequate respiratory protection devices were not immediately or universally available or employed over the course of the rescue and recovery response. Self-contained breathing apparatuses typically used in fire-fighting are not designed for long-term use and generally were not employed at the site beyond the first day of the collapse (Feldman et al. 2004). The types of alternative devices reportedly worn by emergency responders and other workers ranged from surgical masks and ordinary nuisance dust masks, which lack certification for particulate exposure, to disposable N95 respirators and half- and full-

REGULAR ARTICLE

Coffee consumption during pregnancy and the risk of hyperkinetic disorder and ADHD: a prospective cohort study

Karen Markussen Linnet (kmlinnet@ki.au.dk)[1,2], Kirsten Wisborg[1], Niels Jørgen Secher[1,3], Per Hove Thomsen[2], Carsten Obel[1], Søren Dalsgaard[2], Tine Brink Henriksen[1]

1.Perinatal Epidemiology Research Unit, Departments of Obstetrics and Paediatrics, Aarhus University Hospital, Skejby, Denmark
2.Psychiatric Hospital for Children and Adolescents, Aarhus University Hospital, Denmark
3.Department of Obstetrics and Gynaecology, Hvidovre Hospital, Copenhagen University Hospital, Denmark

Abstract

Aim: Based on hypotheses from experimental studies, we studied the association between intrauterine exposure to coffee and the risk of clinically verified hyperkinetic disorder and attention-deficit hyperactivity disorder (ADHD).

Methods: A cohort study with prospectively collected data from the Aarhus Birth Cohort, Denmark. We included 24 068 singletons delivered between 1990 and 1998. Linkage was performed with three Danish longitudinal registers: The Danish Psychiatric Central Register, The Integrated Database for Labour Market Research and The Danish Civil Registration System. We identified 88 children with hyperkinetic disorder and ADHD. Information about coffee consumption during pregnancy was obtained at 16 weeks of gestation from self-administrated questionnaires. Potential confounding factors were evaluated using Cox regression analyses.

Results: We found that intrauterine exposure to 10 or more cups of coffee per day was associated with a threefold increased risk of hyperkinetic disorder and ADHD. After adjustments for a number of confounding factors, the risk decreased and became statistically insignificant (RR 2.3, 95% CI 0.9–5.9).

Conclusion: Prenatal exposure to high levels of coffee did not significantly increase the risk of clinically verified hyperkinetic disorder and ADHD in childhood.

Some Terminology

- The terms "prospective," "longitudinal," and "follow-up" study (contrasted with "retrospective" for case control studies) have been used synonymously for cohort studies but this terminology is slowly being abandoned and replaced with the term "cohort study"

- Cohort studies are also designated by the timing of the data collection (retrospectively or prospectively) in relationship to the investigator's time
  - Historical, retrospective, and nonconcurrent: collect data on <u>events</u> that have already occurred
  - Prospective: most widespread use is to refer to studies in which the investigators observe occurrence of events
  - Note: exposures and outcome may or may not have already occurred

- Single vs. double cohort

Variants of cohort design
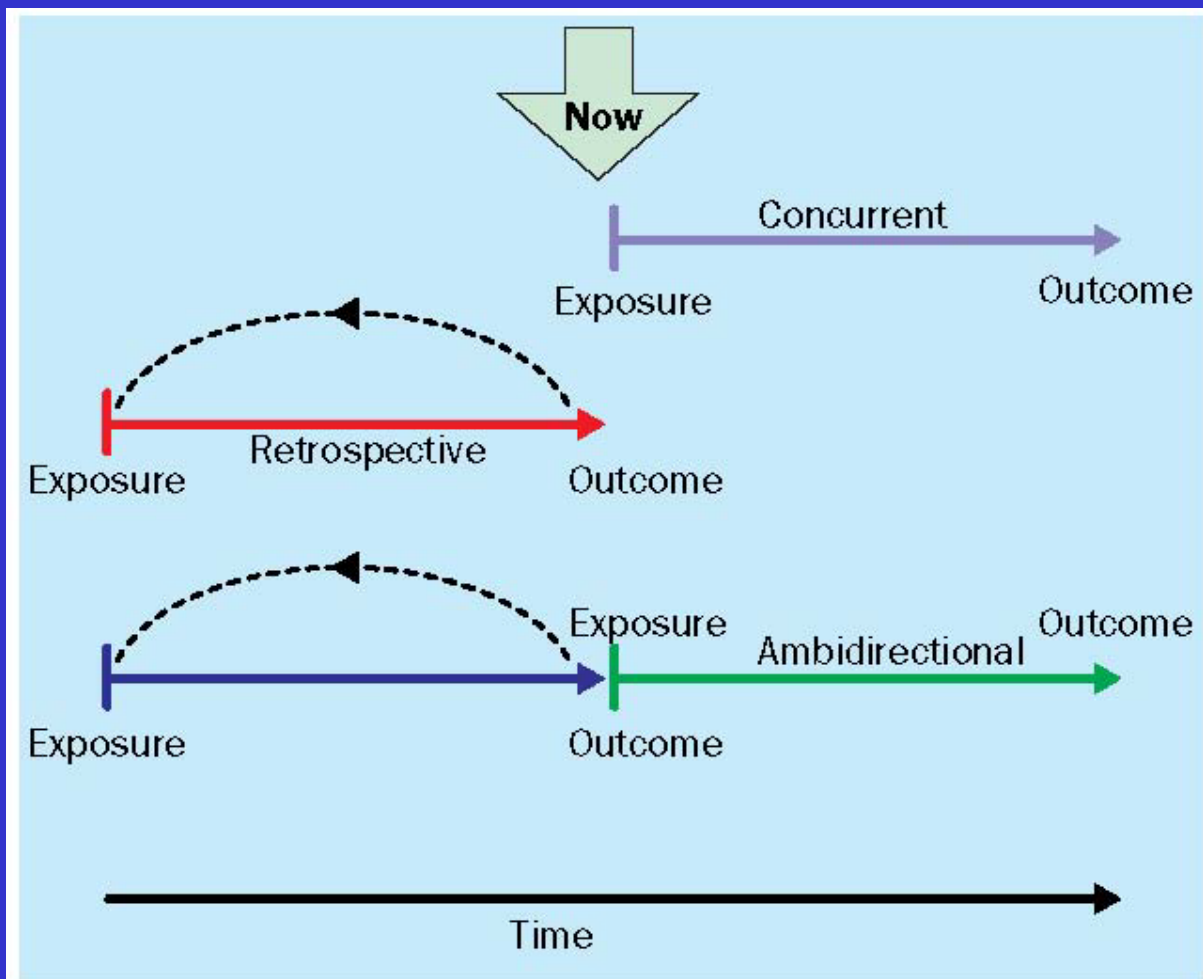
Figure 2: **Schematic diagram of concurrent, retrospective, and ambidirectional cohort studies**

Prospective cohort design

Prospective

2008

2018

2028

Defined Population

N O N - R A N D O M I Z E D

Exposed

Non-Exposed

Disease

No Disease

Disease

No Disease

Gordis: Epidemiology, 4th Edition.
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Time frame for a hypothetical prospective cohort study begun in 2008.

Retrospective cohort design

Gordis: Epidemiology, 4th Edition.
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Time frame for a hypothetical retrospective cohort study begun in 2008.

Example of a retrospective cohort study

Papers

Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976

Janet W Rich-Edwards, *instructor*,[b] **Meir J Stampfer**, *professor*,[d] **JoAnn E Manson**, *associate professor*,[b] **Bernard Rosner**, *professor*,[c] **Susan E Hankinson**, *assistant professor*,[c] **Graham A Colditz**, *professor*,[c] **Charles H Hennekens**, *professor*,[b] **Walter C Willet**, *professor*[d]

▶ **Abstract**

- ▲ Top
- · Abstract
- ▼ Introduction
- ▼ Subjects and methods
- ▼ Results
- ▼ Discussion
- ▼ References

Objective: To examine the association between birth weight and non-fatal adult cardiovascular disease while controlling for potential confounders such as socioeconomic group and adult lifestyle.

Design: Retrospective self report of birth weight in an ongoing longitudinal cohort of nurses followed up by postal questionnaire every two years.

Setting: Nurses' health study, a cohort of 121 700 women followed up since 1976.

Main outcome measures: Non-fatal cardiovascular disease, including myocardial infarction, coronary revascularisation, and stroke.

Results: Among the 70 297 women free of cardiovascular disease at baseline who reported birth weight in the 1992 questionnaire there were 1309 first cases of non-fatal cardiovascular disease. Increasing birth weight was associated with decreasing risk of non-fatal cardiovascular disease. There were 1216 first cases of non-fatal cardiovascular disease among women who were singletons and had been born full term; their relative risks adjusted for several cardiovascular risk factors were 1.49 (95% confidence interval 1.05 to 2.10) for birth weight <2268 g (<5 lb 0 oz); 1.25 (0.98 to 1.61) for birth weight 2268-2495 g (5 lb 0 oz to 5 lb 8 oz); 1.12 (0.98 to 1.27) for birth weight >2495-3175 g (>5 lb 8 oz to 7 lb 0 oz); 1.00 (referent) for birth weight >3175-3856 g (>7 lb 0 oz to 8 lb 8 oz); 0.96 (0.80 to 1.15) for birth weight >3856-4536 g (>8 lb 8 oz to 10 lb 0 oz); and 0.68 (0.46 to 1.00) for birth weight >4536 g (>10 lb 0 oz) (P value for trend=0.0004). The inverse trend was apparent for both coronary heart disease and stroke.

Conclusions: These data provide strong evidence of an association between birth weight and adult coronary heart disease and stroke.

How was exposure determined?

•In 1992 the women indicated their birth weight in categories of pounds. These were not sure, <5 lb, 5 lb to 5½ lb, >5½ lb to 7 lb, >7 lb to 8½ lb, >8½ lb to 10 lb, and >10 lb.

•The women also said whether they had been born full term or two or more weeks prematurely and whether they were one of a multiple birth (hereafter referred to as twins).
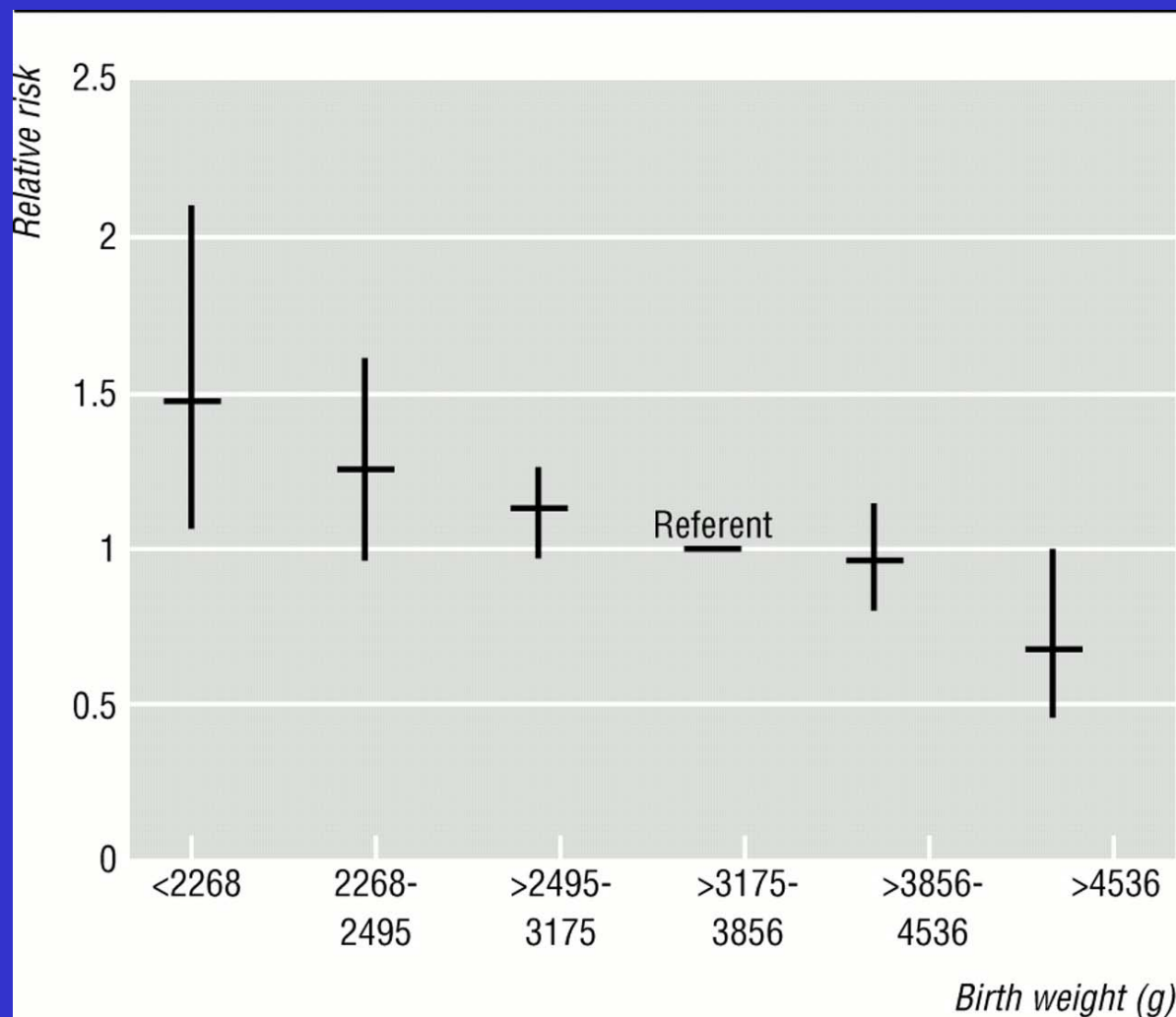
Validation of self reported birth weight

•The validity of self reported birth weights was tested among a younger cohort of female nurses aged 27-44 years

• Birth weight was obtained from 220 state birth certificates, and 70% of participants reported the same birth weight category as their birth certificate

•The Spearman correlation between categories of self reported and recorded birth weight was 0.74

How was outcome determined?

- Because we obtained information in 1992 on birth weight we were able to consider only non-fatal cardiovascular end points that occurred between the 1976 and 1992 questionnaires.
- Permission to review medical records was sought from participants who reported a non-fatal myocardial infarction or stroke.
- The records were reviewed by doctors who were blind to the risk factors of the participants.
- Non-fatal myocardial infarctions and strokes for which we could not obtain hospital records but which required admission and were corroborated by additional information in a letter or from a telephone interview were classed as probable events.

Fig 1 Relative risks with 95% confidence intervals for non-fatal cardiovascular disease by birth weight

(Single) Cohort Study Design

Defined Population

No Randomization

Exposed

Non Exposed

Diseased

Non-diseased

Diseased

Non-diseased

(Double) Cohort Study Design

```
        ┌──────────┐                      ┌──────────────┐
        │ Exposed  │                      │ Non Exposed  │
        └──────────┘                      └──────────────┘
         ┌──────┴──────┐                  ┌──────┴──────┐
┌──────────┐  ┌──────────────┐   ┌──────────┐  ┌──────────────┐
│ Diseased │  │ Non-diseased │   │ Diseased │  │ Non-diseased │
└──────────┘  └──────────────┘   └──────────┘  └──────────────┘
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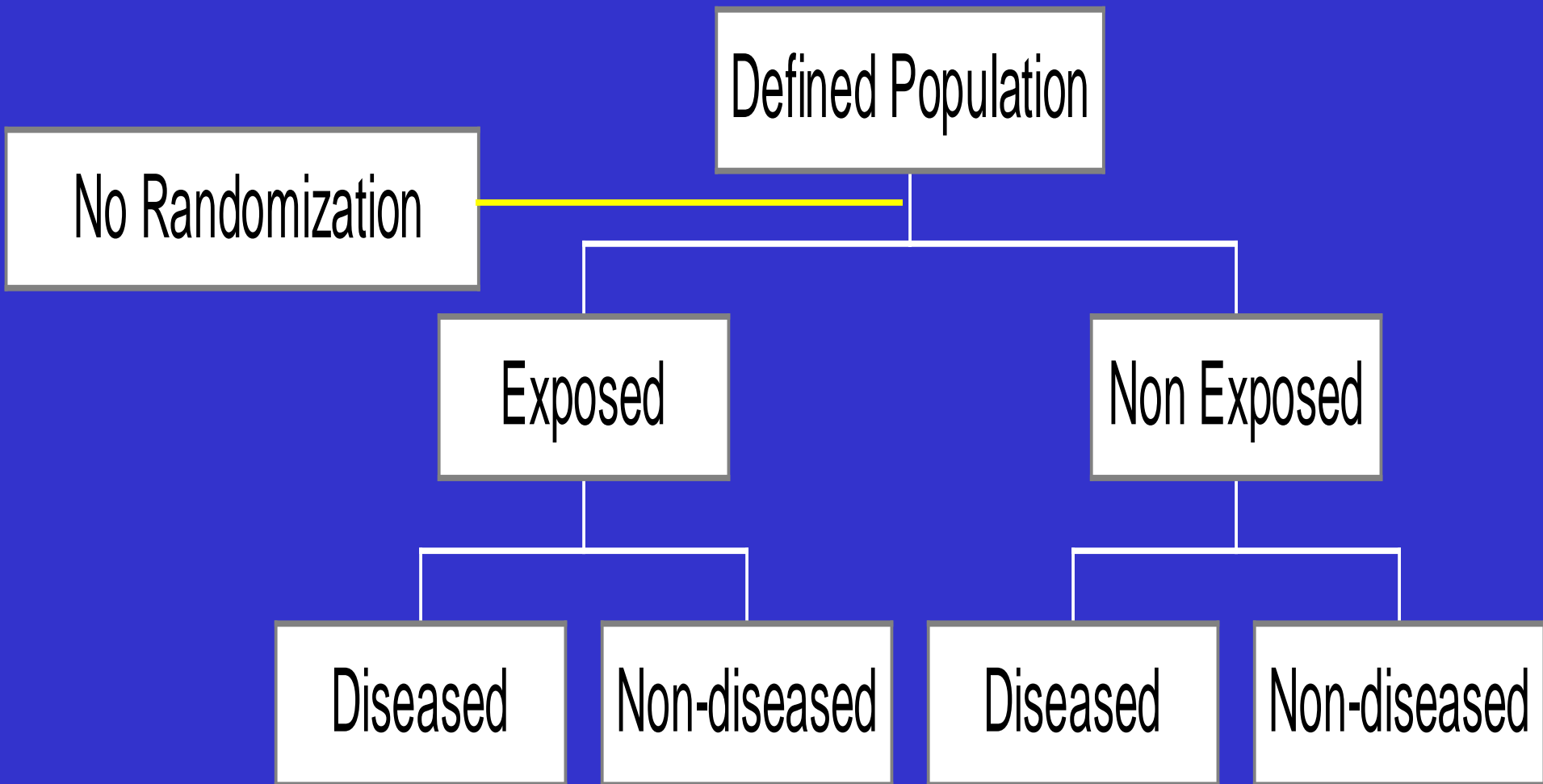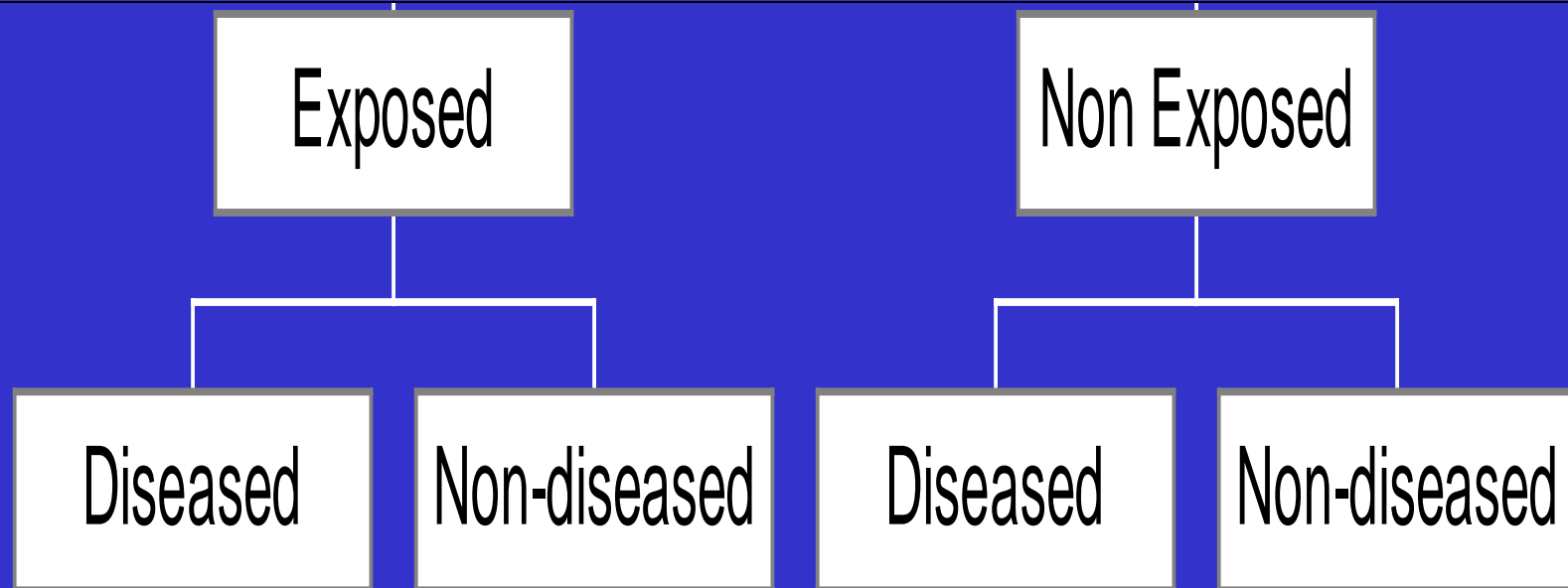
Methodologic advances in the cohort design

- Cohort studies have greatly evolved over time

- The challenge of coping with temporally changing exposures and covariates can now be tackled using increasingly sophisticated designs for longitudinal data analysis.

  - The paucity of software and hardware able to cope with such analyses prevented their widespread application until only recently
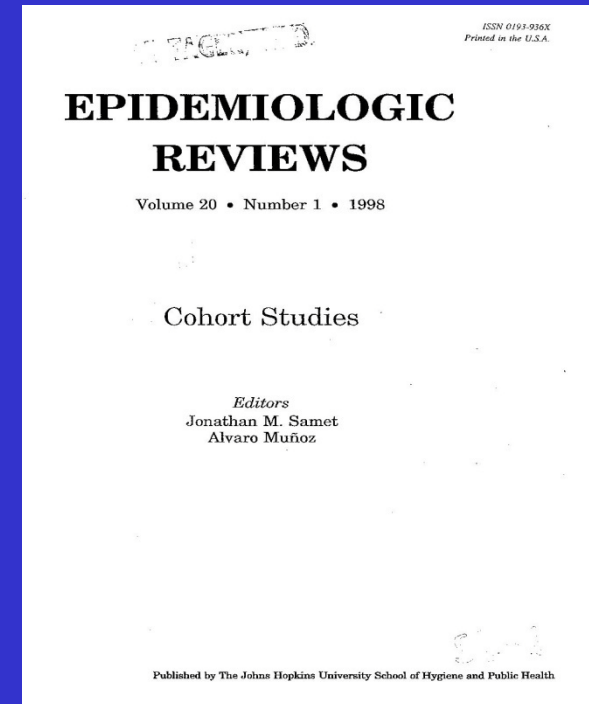
Modern era of cohort research (begins late 1940s, early 1950s)

- Landmark studies (some continue today)
    - Framingham heart study
    - Japanese atomic bomb survivors
    - British doctors cohort study
- Key features of these cohort studies
    - Size
    - Richness of the data
    - Sustained follow-up data over <u>decades</u>

Framingham Heart Study

- Begun in 1948 to address rising incidence of CVD

- Key features in its success

  - Selection of a small and cooperative community

  - Sustained NIH support (maintained it as an intramural project)

  - Rigorous and standardized protocols for data collection

  - Third generation of family members now enrolled (grandchildren of the original cohort!)

  - Methodologic advances were forthcoming to permit useful evaluation of such longitudinal data

    - Example: first application of discriminant analysis in epidemiology in 1967 (Truett et al. A multivariate analysis of the risk of coronary heart disease in Framingham. J Chronic Dis 1967; 20:511-24)—predicted 12-year probability of developing coronary heart disease based on levels of seven risk factors.

  - >1200 publications over 50 years!

Directions | Contact Info | Search

FRAMINGHAM HEART STUDY

A Project of the National Heart, Lung and Blood Institute and Boston University

| About FHS | Participants | FHS Investigators | Risk Score Profiles | FHS Bibliography | For Researchers |

Three generations of participants.

The dedication of our thousands of participants has made, and continues to make, our rigorous epidemiologic research possible.

National **Heart Lung and Blood** Institute
Boston University

Welcome to the Framingham Heart Study

In 1948, the Framingham Heart Study embarked on an ambitious project in health research to identify the common factors that contribute to cardiovascular disease by following its development over a long period of time in a large group of participants. >>

Phillip Wolf, MD, Principal Investigator, and Dan Levy, MD, Director, with the staff of the Framingham Heart Study.

Genomic Research at the Framingham Heart Study (SHARe Study)
VIEW SHARe WEBSITE >>

Recently the Honorable Michael O. Leavitt, United States Secretary of Health and Human Services, expressed the nation's appreciation to participants of the Framaingham Heart Study. Their many years of dedication has made possible the SHARe (SNP Health Association Research) project, the new state of the art phase of scientific discovery previously announced in the Winter 2007 newsletter. The SHARe project was officially launched with a nationwide presentation in Washington on October 1, 2007.
MORE >>

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Directions | Contact Info | Site Map | Site created by Schenkel/Stegman Communications Design
Site edited by Esta Shindler. Updated monthly. Last updated September 24, 2008

Original Cohort

The Original Cohort of the Framingham Heart Study consisted of 5,209 respondents of a random sample of 2/3 of the adult population of Framingham, Massachusetts, 30 to 62 years of age by household, in 1948. Exam 28 for the Original Cohort ended in December of 2005. Exam 29 for the Original Cohort began in April of 2006.

AGE–SEX DISTRIBUTION AT ENTRY (1948)

Age	29–39	40–49	50–62	Totals
Men	835	779	722	2,336
Women	1,042	962	869	2,873
Totals	1,877	1,741	1,591	5,209

Offspring Cohort

The Offspring Study was initiated in 1971 when the need for establishing a prospective epidemiologic study of young adults was recognized. A sample of 5,124 men and women, consisting of the offspring of the Original Cohort and their spouses was recruited. Offspring Exam 8 began in March 2005.

AGE–SEX DISTRIBUTION AT ENTRY (1971)

Age	<10	10–19	20–29	30–39	40–49	50–59	60–70	Totals
Men	0	126	543	789	694	293	38	2,483
Women	6	113	692	835	740	242	13	2,641
Totals	6	239	1,235	1,624	1,434	535	51	5,124

Third Generation Cohort (Gen III)

A recent major component of the Framingham Heart Study protocol has been the enrollment and examination of a third generation of participants which will provide greater resources of phenotypic and genotypic information. During Offspring Exam Cycles 6 and 7, the Offspring participants were asked to update information about their children. To assess interest in participation prior to the start of clinic exams, 5,500 letters and response cards were sent in November 2001 to prospective third generation participants who had at least one parent in the Offspring Study and would be at least 20 years old by the close of the first exam cycle. Later an additional 1,241 invitation letters were sent. A prioritization of the recruitment list was prepared. Considerations were given to family size, completeness of data, stored DNA and responsiveness of the Gen III members of the families.

By consenting to and completing Exam 1 of Gen III, the participant was considered enrolled in the Framingham Heart Study Gen III. Special efforts were being made to complete sibships and families in the course of enrollment. A recruitment target of 4,095 Gen III participants was achieved by July of 2005. The details of clinic attendance for Gen III are described in the table to follow.

GEN3: AGE–SEX DISTRIBUTION AT ENTRY (THROUGH 2005)

Age	19	20–29	30–39	40–49	50–59	60–69	70–79	Totals
Men	4	220	656	737	276	19	1	1,913
Women	3	262	759	848	293	16	1	2,182
Totals	7	482	1,415	1,585	569	35	2	4,095

Japanese atomic bomb survivor study

- Addressed consequences of ionizing radiation exposure
- Unlike Framingham study (which was designed to test multiple hypotheses) this study had only one goal: to address the consequences of ionizing radiation exposure
- Radiation doses for sampled survivors were reconstructed and they were entered into a cohort study with regular medical exams
- This study provides the underpinnings of radiation standards worldwide

Japanese atomic bomb survivor study (cont.)

- Some findings:
  - Acute leukemia peaked about 1952 and then began to decline
  - By 1960 excesses of solid tumors were noted
  - The study's design encouraged methodological developments related to measurement of time and age-dependent effects, interaction of radiation with other factors, and the consequences of measurement error (reviewed in: Samet J. Epidemiologic studies of ionizing radiation and cancer: past successes and future challenges. Environ. Health Perspect 1997; 105(suppl4): 883-9

Doll and Hill cohort study of British physicians

- Was a follow-up of initial observations from (mistrusted) case-control studies suggesting a very strong association between smoking and lung cancer
- Began in 1951, continues in 2005
- 40 year follow-up reported in 1994 (Doll et al. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 1944; 309: 901-11)

Medscape
Medical News

Golden anniversary: data on 50 years of smoking in British docs

Jun 23, 2004
London, UK - A British study on smoking and mortality in male doctors has yielded new information, 50 years after it began. The latest results appear online June 22, 2004 in *BMJ* [1], along with the preliminary findings from the study, which were first published in the journal in 1954 [2].

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Lead author on both the first paper and the new one, 91-year-old **Sir Richard Doll** (Clinical Trial Service Unit, Oxford University, UK), spoke at a press conference in London yesterday, accompanied by fellow author **Sir Richard Peto** (Oxford University), who has worked on the study for the past 30 years.

Sir R Peto   **Sir R Doll**

In an editorial accompanying publication of the 2 papers [3], epidemiologist **Dr Meir Stampfer** (Harvard School of Public Health, Boston, MA), says: The 2 Sir Richards have been world leaders in the study of the health effects of smoking, and this latest contribution represents a stunning achievement."

The British doctors' study—as it became known—has followed almost 35 000 male doctors born until 1930, who were monitored and periodically asked about their smoking habits. The last questionnaire was completed in 2001; 5900 of the original population were still alive but only 134 of them were still smoking. "A lot were killed by the habit, but a lot gave up," Doll commented. He himself smoked until the age of 37.

Doll and Hill cohort study of British physicians (cont.)

- Strengths of the study:
  - Selection of a cooperative population that could easily be followed for mortality (public data) and smoking status (mailed questionnaire)
- This study , along with 7 other prospective cohort studies, were available for review by the Surgeon General's advisory committee (US Dept. HEW, Public Health Services. Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service. Washington, DC: US GPO, 1964)

The New York Times — Obituaries

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Sir Richard Doll Dies at 92; Linked Smoking to Illnesses

By **LAWRENCE K. ALTMAN**
Published: July 26, 2005

Sir Richard Doll, a British epidemiologist whose pioneering studies lasting more than 50 years linked smoking to lung cancer, emphysema, heart attacks and many other ailments, died on Sunday in John Radcliffe Hospital in Oxford, England. He was 92.

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Sir Richard worked until his death, which was from acute heart failure, said Sir Richard Peto, a colleague for more than 30 years. "He was one of the greatest epidemiologists of our time," he said yesterday. "His work prevented millions of deaths and will prevent tens of millions more deaths this century."

Sir Richard's research extended to many other areas.

In an interview in a medical journal, he said that is second-most-important work was showing that even small doses of ionizing radiation could produce cancer.

Damian Dovarganes/Associated Press

The era of large, focused, cohorts (1970's +)

- NIH took the lead in establishing multicenter, prospective cohort studies, especially in the area of cardiovascular disease:

  - Atherosclerosis Risk in Communities Study (ARIC)
  - Cardiovascular Health Study
  - Nurses Health Study (NHS)

- These studies attempted to increase external validity through their multi-center design

The era of large, focused, cohorts (1970's +) cont.

- Nurses' Health Study (began 1976)
  - Original goal was to evaluate risks of oral contraceptives
  - Has become one of the principal sources of observational data on diet and chronic diseases
  - Questionnaires are periodically mailed out to thousands of nurses

Nurses' Health Study

What happens to my questionnaire after I mail it in?

Welcome to the Channing Laboratory, home of the Nurses' Health Study. This is where all your questionnaires arrive to be sorted, counted, and processed by our research staff. We receive as many as 10,000 completed questionnaires each day.

To handle all of this mail we employ approximately 25 Research Data Coders who are responsible for sorting, counting, and coding the incoming questionnaires.

This is a typical day's mail after it has been sorted and counted into bundles of 50 surveys.

http://www.channing.harvard.edu/nhs/gallery/index.shtml

Nurses' Health Study

After each day's mail is counted, it is stored in our filing system to await coding. Here, Project Manager Gary Chase, shows the new staff how to store the newly arrived envelopes.

Finally, the mail is away.

top
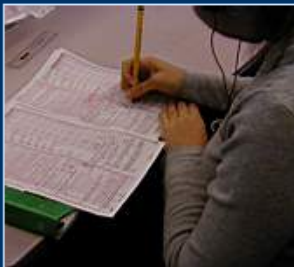
The next step is to process the forms. The staff open the mail and carefully review each form. The Coders check for incomplete surveys, make sure each form is filled out in pencil (so that the marks will be captured by our scanner), and assign codes for cereal, vitamin, and margarine brands.

http://www.channing.harvard.edu/nhs/gallery/index.shtml

Nurses' Health Study

When we encounter a form which needs extra attention, the staff places the form in a specially labeled "Problem Box" to await review by a senior staff member or investigator.

Sometimes it is necessary to write back to the respondent to clarify an answer.

Capturing your answers correctly is our main goal.

After a form is fully coded, it is ready to be scanned. Shown here, our scanner can read as many as 7,000 forms per hour. In addition to converting the pencil-filled bubbles into numeric data, the scanner captures a digital image of each form which we archive and keep forever.

Following scanning, the data is then reviewed in our verification process. In this step, a senior staff member uses a computer program to examine the data, looking for errors or omissions. The program displays the data so that the operator can compare the answers that were captured by the scanner against the actual paper questionnaire. In this way any missed marks or questionable answers can be caught before the data is permanently saved.

http://www.channing.harvard.edu/nhs/gallery/index.shtml

Snail Mail to Online Questionnaires!

Nurses'
Health Study III
"Linked to the past. Looking to the future."

Welcome to the Nurses' Health Study III Questionnaire website. Thank you for participating in this important new study of women's health.

To start, enter your **Login ID** and **Password** from your invitation letter.

Participant ID: _____

Password: _____

Login

Thanks for being a participant in NHS3. Please click here to send us an e-mail or call us at (617) 525-2279, 9am-4pm Eastern time.

The information you give us will remain strictly confidential and will be used only for medical statistical purposes.

For information on confidentiality and privacy please click here.

Combined impact of lifestyle factors on mortality: prospective cohort study in US women

Rob M van Dam, assistant professor of medicine,[1,2] Tricia Li, research fellow,[1] Donna Spiegelman, professor of epidemiology and biostatistics,[3,4] Oscar H Franco, researcher,[5] Frank B Hu, professor of nutrition and epidemiology[1,2,3]

[1]Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115, USA

[2]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston MA 02115

[3]Department of Epidemiology, Harvard School of Public Health

[4]Department of Biostatistics, Harvard School of Public Health

[5]Unilever Corporate Research, Sharnbrook, Bedfordshire MK44 1LQ

Correspondence to: R van Dam rvandam@hsph.harvard.edu

ABSTRACT

Objective To evaluate the impact of combinations of lifestyle factors on mortality in middle aged women.

Design Prospective cohort study.

Setting Nurses' health study, United States.

Participants 77 782 women aged 34 to 59 years and free from cardiovascular disease and cancer in 1980.

Main outcome measure Relative risk of mortality during 24 years of follow-up in relation to five lifestyle factors (cigarette smoking, being overweight, taking little moderate to vigorous physical activity, no light to moderate alcohol intake, and low diet quality score).

Results 8882 deaths were documented, including 1790 from cardiovascular disease and 4527 from cancer. Each lifestyle factor independently and significantly predicted mortality. Relative risks for five compared with zero lifestyle risk factors were 3.26 (95% confidence interval 2.45 to 4.34) for cancer mortality, 8.17 (4.96 to 13.47) for cardiovascular mortality, and 4.31 (3.51 to 5.31) for all cause mortality. A total of 28% (25% to 31%) of deaths during follow-up could be attributed to smoking and 55% (47% to 62%) to the combination of smoking, being overweight, lack of physical activity, and a low diet quality. Additionally considering alcohol intake did not substantially change this estimate.

Conclusions These results indicate that adherence to lifestyle guidelines is associated with markedly lower mortality in middle aged women. Both efforts to eradicate cigarette smoking and those to stimulate regular physical activity and a healthy diet should be intensified.

The proportion of deaths that is attributable to lifestyle factors has been estimated by Mokdad and colleagues and in the global burden of disease study, using data on relative risks and the prevalence of risk factors from multiple sources.[8][9] As a result of this broad approach, the imprecision and potential biases affecting the results were less transparent and the analysis of lifestyle factors was less detailed than can be achieved in a well characterised prospective cohort study. In a cohort study in 11 European countries, an estimated 60% of deaths from all causes during 10 years of follow-up could be attributed to lack of adherence to non-smoking, a healthy diet, regular physical activity, and moderate alcohol intake.[10] However, this study included only 2339 participants, who were elderly and mostly male, and whether the findings apply to younger populations and women thus remains unclear. We therefore examined combinations of lifestyle factors in relation to cancer, cardiovascular, and all cause mortality during 24 years of follow-up among middle aged women who participated in the nurses' health study. We also estimated population attributable risks, the proportion of deaths during follow-up that could potentially have been avoided by adherence to lifestyle guidelines.

METHODS

Study population

The nurses' health study is a prospective cohort study that was established in 1976 when 121 700 female

Multicenter AIDS Cohort Study (MACS)

- Began in 1984 with a cohort of approximately 5,000 gay men in four cities
- Study began before HIV was identified as the cause of AIDS
- Collected complete clinical data and stored blood specimens every 6 months
- Used repeatedly to study risk factors for HIV infection, progression, and prognosis

Methodologic advances driven by cohort studies

- Cohort data analysis fostered collaborations between epidemiologists and biostatisticians
- One key advance was the development of sampling methods for efficiently addressing the relation between exposure and outcome (especially valuable when outcomes are infrequent)
  - E.g. widespread use of nested case-control designs
- Another key advance was development of sophisticated multivariable methods to address confounding and correlations between repeated measures

Methodologic advances driven by cohort studies (cont.)

- Example: nested case-control study compares the exposure history of the cases within a cohort to controls in the cohort sampled from the <u>time at which the cases developed</u>

  - Nested case control studies are usually analyzed using conditional logistic regression

- Example: case-cohort study compares covariate data for cases with that of a random sample of controls drawn from the <u>start of the study</u>

  - Case-cohort studies are usually analyzed with Cox regression(with staggered entries and robust methods for calculation of standard errors)

TABLE 1. Overview of analytical methods for cohort studies

| Outcome	Summary measure	Comparison		Measure of association
		Exposed/unexposed (2-sample)	Multiple (regression)	
Events in person-years	Incidence rate	$(O-E)^2/var$	Poisson	Relative incidence
Time to event	Kaplan-Meier/maximum likelihood estimates	Logrank or Mantel-Haenszel/likelihood ratio test	Proportional hazards/ parametric	Relative hazard/relative percentile or time
Time to event; exposures changing	Extended Kaplan-Meier	Extended logrank	Proportional hazards, staggered entries	Relative hazard
Case in nested case-control	Proportion exposed	Paired chi-square or McNemar	Conditional logistic	Odds ratio
Case in nested case-cohort	Proportion exposed	(Robust) logrank	Proportional hazards, staggered entries	Relative hazard
Intermediate outcome repeatedly measured	Change		Regression for correlated data; marginal, conditional, random effects	Differences in change over time

Data analysis in cohort studies in the 1970's

- Prior to the 1970's, analyses of cohort data were based primarily on life-table methods; binary variables were the principal outcomes

- Methods extended to cohort analysis (such as discriminant analysis and logistic regression) did not explicitly incorporate time

- Seminal paper by Cox (J.Royal Stat Sci 1972;B34:187-202) provided the basis for what is known as proportional hazards (Cox) regression

- Poisson regression methods were extended in the 1970's for the analysis of events in person-years data structures
  - Particularly useful for the analysis of trends and changes in incidence of disease over calendar time
  - Of great utility for data in which specific time origin is not well-defined

Data analysis in cohort studies in the 1980's and 1990's

- Development of techniques for longitudinal data analysis: the analysis of markers of disease progression observed repeatedly (e.g. blood pressure, weight, etc.)

- Four broad categories of longitudinal data analysis with repeated measures:
    - Marginal models
    - Transitional models
    - Random effects models
    - Regression trees ("CART" refers to regression and classification trees)

Data analysis advances in the 1990's and 2000's

- Unified framework for linear models articulated under which linear, logistic, Poisson, and many survival regression models could be viewed as specific cases of generalized linear models ("GLM")
  - Extensions of this model permit relaxation of the assumptions previously required and triggered the development of new techniques (such as quasi-likelihood)
  - These new GLM methods can:
    - Cope with more complicated variance structures (e.g. correlated data)
    - Handle nuisance correlations with robust methods for approximating estimated standard errors
- Mixed and hierarchical models (multi-level models)
- Models that handle time dependent variables
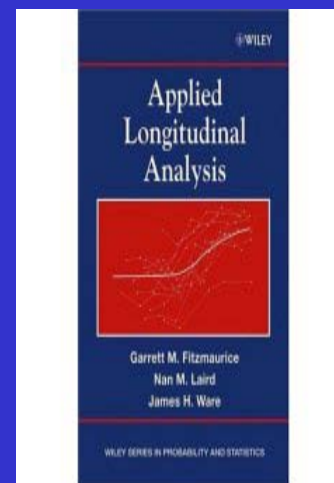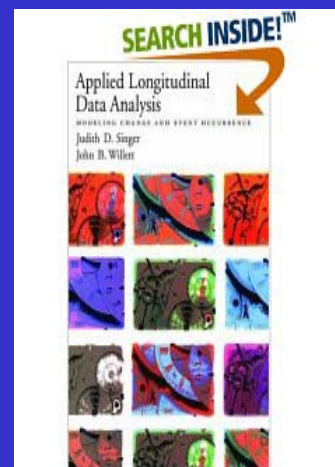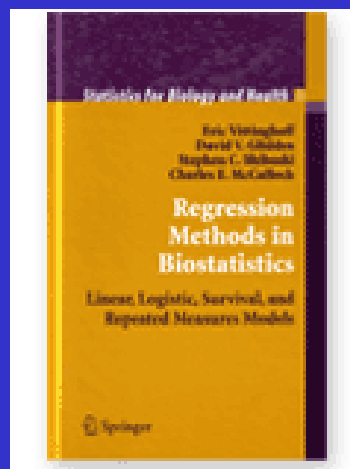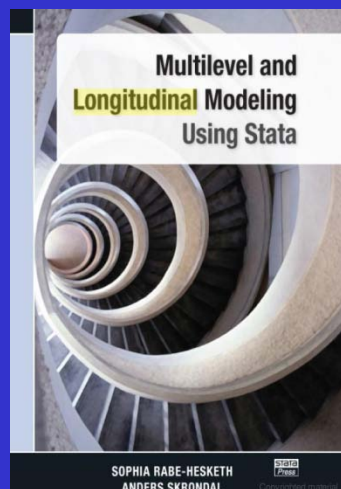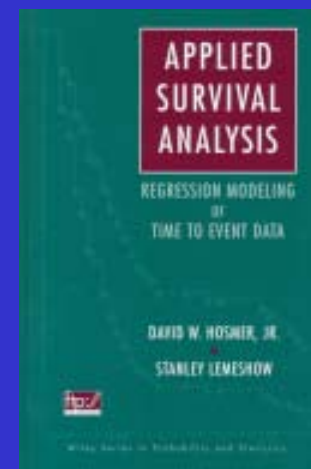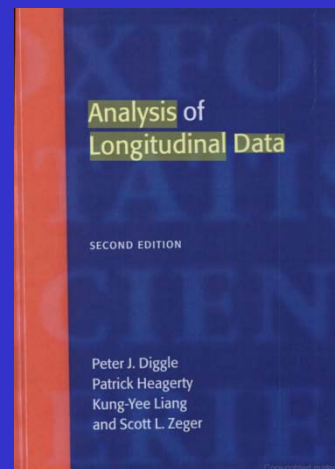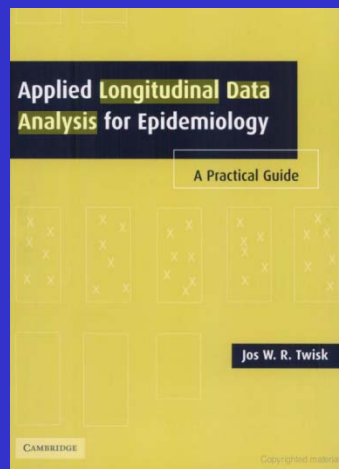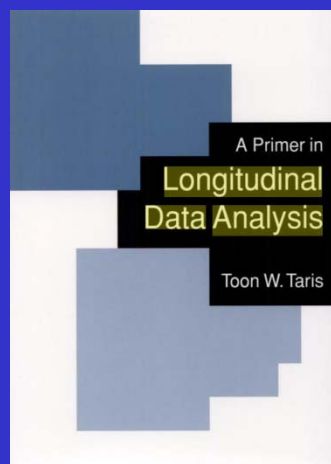
Bias in cohort studies

- Selection bias
- Information bias
- Confounding

POTENTIAL BIASES IN COHORT STUDIES

A number of potential biases must be either avoided or taken into account in conducting cohort studies. The major biases include the following:

1. *Bias in assessment of the outcome:* If the person who decides whether disease has developed in each subject also knows whether that subject was exposed, and if that person is aware of the hypothesis being tested, that person's judgment as to whether the disease developed may be biased by that knowledge. This problem can be addressed by masking the person who is making the disease assessment and also by determining whether this person was, in fact, aware of each subject's exposure status.

2. *Information bias:* If the quality and extent of information obtained is different for exposed persons than for nonexposed persons, a significant bias can be introduced. This is particularly likely to occur in historical cohort studies, in which information is obtained from past records. As we discussed with regard to randomized trials, in any cohort study, it is essential that the quality of the information obtained be comparable in both exposed and nonexposed individuals.

3. *Biases from nonresponse and losses to follow-up:* As was discussed in connection with randomized trials, nonparticipation and nonresponse can introduce major biases that can complicate the interpretation of the study findings. Similarly, loss to follow-up can be a serious problem: If people with the disease are selectively lost to follow-up, the incidence rates calculated in the exposed and nonexposed groups will clearly be difficult to interpret.

4. *Analytic bias:* As in any study, if the epidemiologists and statisticians who are analyzing the data have strong preconceptions, they may unintentionally introduce their biases into their data analyses and into their interpretation of the study findings.

Selection bias in cohort studies

- Examples:
  - Bias in using the general population as a comparison group for occupational cohorts
  - Bias due to differential drop-out rates among exposed and unexposed
    - E.g. cohort study on progression to AIDS

Selection Bias: Cohort Studies

Example: Cohort study of progression to AIDS: IV drug users (IDU) vs homosexual men

- In general, getting sicker is a common reason for loss to follow-up
- Therefore, persons who are lost to follow-up have different AIDS incidence than those who remain (i.e., informative censoring)
- In general, IDU more likely to become loss to follow-up - at any given level of feeling sick
- Therefore, the degree of informative censoring differs across exposure groups (IDU vs homosexual men)
- Results in selection bias: underestimates the incidence of AIDS in IDU relative to homosexual men

Jeff Martin, UCSF

Selection Bias: Cohort Studies

Probability of being AIDS-free

Time

Effect of informative censoring in homosexual male group

Effect of informative censoring in IDU group

Survival assuming no informative censoring and no difference between IDU and homosexual men
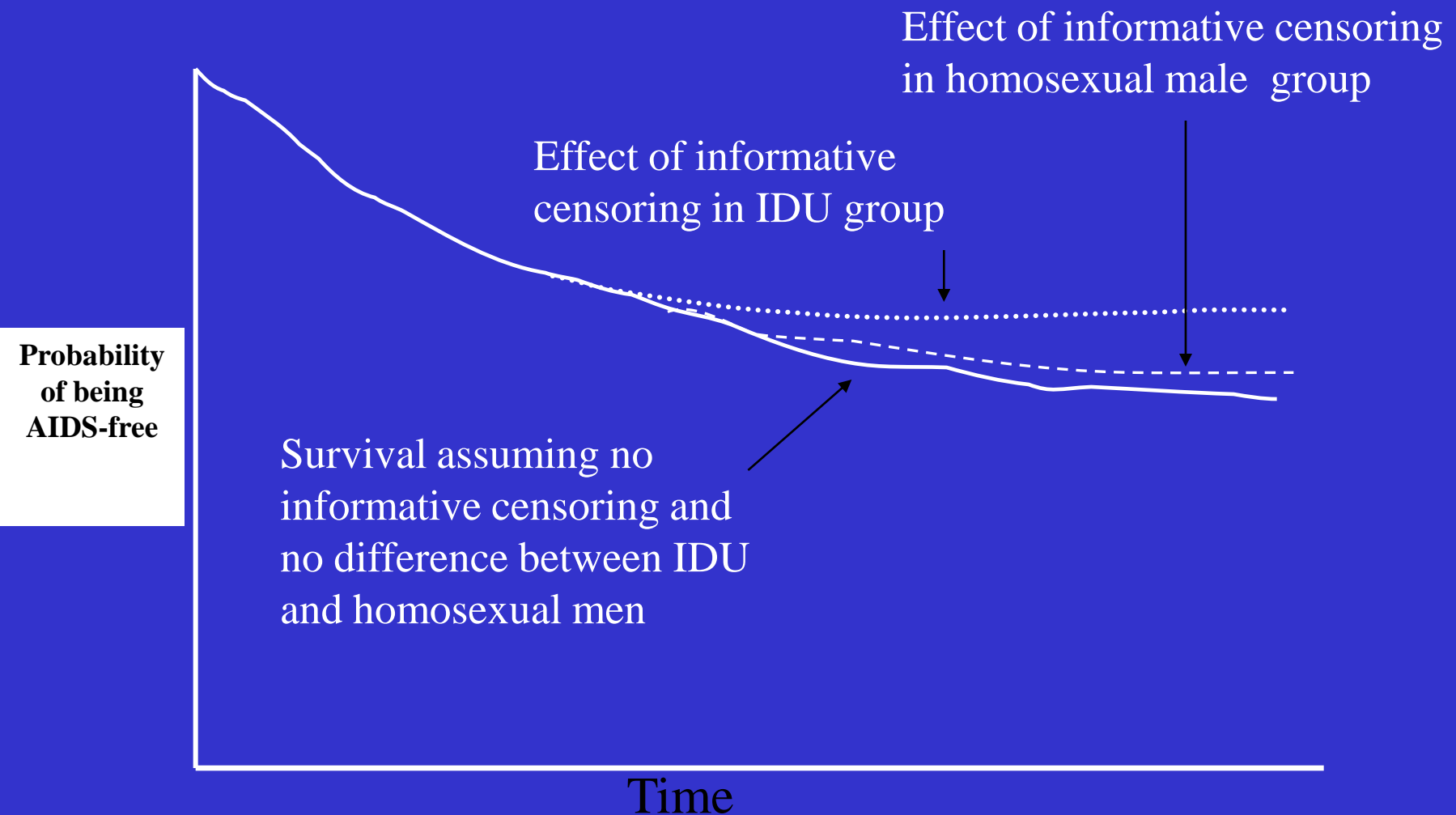
Information bias in cohort studies

- Sources:
  - Misclassification of exposure at baseline (not likely to be influenced by outcome status)
  - Changes in exposure status over time (time-dependent covariates; dynamic exposures)
  - Ascertainment of outcomes during follow-up (which can be influenced by knowledge of exposure status: "detection bias" or "outcome identification bias" or "diagnostic suspicion bias")
    - Clinical example: pathologist more likely to use the term "alcoholic cirrhosis" when evaluating a borderline liver specimen if the pathologist knows the patient is alcoholic
    - Another example: nephrologists sent simulated case histories in which the patient's race was identified randomly as black or white.
      - The nephrologists were 2x more likely to make a diagnosis of hypertensive end-stage renal disease if the patient was identified as black in the history

Confounding: a key concern with cohort studies

Table 1 Comparison of cohort studies and randomised controlled trials

Item	Cohort studies	Randomised controlled trials
Populations studied	Diverse populations of patients who are observed in a range of settings	Highly selected populations recruited on the basis of detailed criteria and treated at selected sites
Allocation to the intervention	Based on decisions made by providers or patients	Based on chance and controlled by investigators
Outcomes	Can be defined after the intervention and can include rare or unexpected events	Primary outcomes are determined before patients are entered into study and are focused on predicted benefits and risks
Follow-up	Many cohort studies rely on existing experience (retrospective studies) and can provide an opportunity for long follow-up	Prospective studies; often have short follow-up because of costs and pressure to produce timely evidence
Analysis	Sophisticated multivariate techniques may be required to deal with confounding	Analysis is straightforward

Cohort study on HRT and cardiovascular disease

POSTMENOPAUSAL ESTROGEN THERAPY AND CARDIOVASCULAR DISEASE

Ten-Year Follow-up from the Nurses' Health Study

MEIR J. STAMPFER, M.D., GRAHAM A. COLDITZ, M.B., B.S., WALTER C. WILLETT, M.D.,
JoANN E. MANSON, M.D., BERNARD ROSNER, PH.D., FRANK E. SPEIZER, M.D.,
AND CHARLES H. HENNEKENS, M.D.

Abstract *Background.* The effect of postmenopausal estrogen therapy on the risk of cardiovascular disease remains controversial. Our 1985 report in the *Journal,* based on four years of follow-up, suggested that estrogen therapy reduced the risk of coronary heart disease, but a report published simultaneously from the Framingham Study suggested that the risk was increased. In addition, studies of the effect of estrogens on stroke have yielded conflicting results.

Methods. We followed 48,470 postmenopausal women, 30 to 63 years old, who were participants in the Nurses' Health Study and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes.

Results. After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95 percent confidence interval, 0.40 to 0.80); the risk was significantly reduced among women with either natural or surgical menopause. We observed no effect of the duration of estrogen use independent of age. The findings were similar in analyses limited to women who had recently visited their physicians (relative risk, 0.45; 95 percent confidence interval, 0.31 to 0.66) and in a low-risk group that excluded women reporting current cigarette smoking, diabetes, hypertension, hypercholesterolemia, or a Quetelet index above the 90th percentile (relative risk, 0.53; 95 percent confidence interval, 0.31 to 0.91). The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95 percent confidence interval, 0.78 to 1.00) for total mortality and 0.72 (95 percent confidence interval, 0.55 to 0.95) for mortality from cardiovascular disease. The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95 percent confidence interval, 0.65 to 1.45), with no marked differences according to type of stroke.

Conclusions. Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke. (N Engl J Med 1991; 325:756-62.)

Confounding was adjusted using multivariate analysis

Table 2. Relative Risk of Cardiovascular Disease among Current and Former Postmenopausal Hormone Users, as Compared with Those Who Never Used Postmenopausal Hormones, after Adjustment for Age and Multiple Risk Factors.*

Group†	No. of Person-Years	Major Coronary Disease		Fatal Cardiovascular Disease		Total Stroke		Ischemic Stroke		Subarachnoid Hemorrhage	
		No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)
No hormone use	179,194	250	1.0	129	1.0	123	1.0	56	1.0	19	1.0
Current hormone use	73,532										
Adjusted for age	—	45	0.51 (0.37–0.70)	21	0.48 (0.31–0.74)	39	0.96 (0.67–1.37)	23	1.26 (0.78–2.02)	5	0.80 (0.30–2.10)
Adjusted for age and risk factors	—		0.56 (0.40–0.80)		0.61 (0.37–1.00)		0.97 (0.65–1.45)		1.46 (0.85–2.51)		0.53 (0.18–1.57)
Former hormone use	85,128										
Adjusted for age	—	110	0.91 (0.73–1.14)	55	0.84 (0.61–1.15)	62	1.00 (0.74–1.36)	34	1.14 (0.75–1.74)	12	1.42 (0.70–2.90)
Adjusted for age and risk factors	—		0.83 (0.65–1.05)		0.79 (0.56–1.10)		0.99 (0.72–1.36)		1.19 (0.77–1.86)		1.03 (0.47–2.25)

*RR denotes relative risk, and CI confidence interval.

†Women with no hormone use served as the reference category in this analysis. The risk factors included in the multivariate models were age (in five-year categories), cigarette smoking (none, former, current [1 to 14, 15 to 24, and ≥25 cigarettes per day]), hypertension (yes, no), diabetes (yes, no), high serum cholesterol level (yes, no), parental myocardial infarction before the age of 60 (yes, no), Quetelet index (in five categories), past use of oral contraceptives (yes, no), and time period (in five two-year periods).

RCT on HRT and cardiovascular disease

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

Stephen Hulley, MD; Deborah Grady, MD; Trudy Bush, PhD; Curt Furberg, MD, PhD;
David Herrington, MD; Betty Riggs, MD; Eric Vittinghoff, PhD;
for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group

Context.—Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials.

Objective.—To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease.

Design.—Randomized, blinded, placebo-controlled secondary prevention trial.

Setting.—Outpatient and community settings at 20 US clinical centers.

Participants.—A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.

Intervention.—Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and 75% at the end of 3 years.

Main Outcome Measures.—The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered.

Results.—Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each $P<.001$). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38).

Conclusions.—During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary

MANY OBSERVATIONAL studies have found lower rates of coronary heart disease (CHD) in women who take postmenopausal estrogen than in women not receiving this therapy.[1-8] This association has been reported to be especially strong for secondary prevention in women with CHD, with hormone users having 35% to 80% fewer recurrent events than nonusers.[5-12] If this association is causal, estrogen therapy could be an

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For editorial comment see p 650.

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important method for preventing CHD in postmenopausal women. However, the observed association between estrogen therapy and reduced CHD risk might be attributable to selection bias if women who choose to take hormones are healthier and have a more favorable CHD profile than those who do not.[13-15] Observational studies cannot resolve this uncertainty.

Only a randomized trial can establish the efficacy and safety of postmenopausal hormone therapy for preventing CHD.

Confounding was not an issue because of randomization

Table 1.—Baseline Characteristics of HERS Participants (n=2763) by Treatment Group*

| | Treatment Group | | |
| | Estrogen-Progestin (n=1380) | Placebo (n=1383) | P Value |
Characteristic			
Demographics			
Age, mean±SD, y	67±7	67±7	.32
White, %	88	90	.14
Education, mean±SD, y	13±3	13±3	.84
CHD risk factors			
Current smoker, %	13	13	.84
Diabetes on oral medication or insulin, %	19	18	.44
Systolic blood pressure, mean±SD, mm Hg	135±19	135±19	.88
Diastolic blood pressure, mean±SD, mm Hg	73±10	73±10	.89
LDL cholesterol, mean±SD, mmol/L (mg/dL)	3.75±0.96 (145±37)	3.75±0.98 (145±38)	.83
HDL cholesterol, mean±SD, mmol/L (mg/dL)	1.29±0.34 (50±13)	1.29±0.34 (50±13)	.41
Triglyceride, mean±SD, mmol/L (mg/dL)	1.90±0.72 (168±64)	1.86±0.72 (165±64)	.25
Time since last menstrual period, mean ± SD, y	18±8	18±8	.31
Body mass index >27 kg/m^2, %	57	55	.44
Exercise >3 times weekly, %	39	38	.72
No. of drinks per week, mean±SD	1.4±4	1.3±4	.83
General health poor or fair, %	24	24	.94
Postmenopausal estrogen use, %†	24	23	.43
CHD manifestations			
Signs of congestive heart failure, %‡	10	9	.38
Q-wave myocardial infarction, %	17	17	.94
Percutaneous coronary revascularization, %	45	45	.96
Coronary artery bypass graft surgery, %	42	41	.64
Medication use			
Aspirin, %	78	78	.73
β-Blockers, %	33	32	.72
Lipid-lowering medications, %	45	47	.26
Calcium channel blockers, %	55	55	.83
Angiotensin-converting enzyme inhibitors, %	17	18	.57
Diuretics, %	28	28	.79
Multivitamins, %	29	30	.45

B-File #1 provides the full story

THE (B) FILES

Case studies of bias in real life epidemiologic studies

Bias File 1. The Rise and Fall of Hormone Replacement Therapy

Critical appraisal of cohort studies

- Example: The Newcastle-Ottawa Scale
  - **Selection**
    - 1) Representativeness of the exposed cohort
    - 2) Selection of the non exposed cohort
    - 3) Ascertainment of exposure
    - 4) Demonstration that outcome of interest was not present at start of study
  - **Comparability**
    - 1) Comparability of cohorts on the basis of the design or analysis
  - **Outcome**
    - 1) Assessment of outcome
    - 2) Was follow-up long enough for outcomes to occur
    - 3) Adequacy of follow up of cohorts

http://www.lri.ca/programs/ceu/oxford.htm

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   - a) truly representative of the average _____ (describe) in the community ☐
   - b) somewhat representative of the average _____ in the community ☐
   - c) selected group of users eg nurses, volunteers
   - d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   - a) drawn from the same community as the exposed cohort ☐
   - b) drawn from a different source
   - c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   - a) secure record (eg surgical records) ☐
   - b) structured interview ☐
   - c) written self report
   - d) no description

4) Demonstration that outcome of interest was not present at start of study
   - a) yes ☐
   - b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   - a) study controls for _____ (select the most important factor) ☐
   - b) study controls for any additional factor ☐ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   - a) independent blind assessment ☐
   - b) record linkage ☐
   - c) self report
   - d) no description

2) Was follow-up long enough for outcomes to occur
   - a) yes (select an adequate follow up period for outcome of interest) ☐
   - b) no

3) Adequacy of follow up of cohorts
   - a) complete follow up - all subjects accounted for ☐
   - b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ☐
   - c) follow up rate < ____% (select an adequate %) and no description of those lost
   - d) no statement

PLoS MEDICINE

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies

Erik von Elm[1*], Douglas G. Altman[2], Matthias Egger[1,3], Stuart J. Pocock[4], Peter C. Gøtzsche[5], Jan P. Vandenbroucke[6] for the STROBE Initiative

1 Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland, 2 Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom, 3 Department of Social Medicine, University of Bristol, Bristol, United Kingdom, 4 London School of Hygiene and Tropical Medicine, University of London, London, United Kingdom, 5 Nordic Cochrane Centre, Copenhagen, Denmark, 6 Department of Clinical Epidemiology, Leiden University Hospital, Leiden, The Netherlands

STROBE
Checklist
for
Cohort
Studies

http://www.strobe-statement.org

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias

Required readings

- Gordis text:
  - Chapter 9: Cohort studies